Clinical Investigations

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McDermott Will & Emery LLP
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FDLI

Agenda

- Overview
- Investigational Device Exemption (IDE)
- Pre-Submission Meetings and Agreement Meetings
- Key Players, Roles & Responsibilities
- Good Clinical Practice (GCP) Highlights
- Prohibition on Promotion / Commercialization
- Bioresearch Monitoring (BIMO) and Enforcement Actions
- Other Issues & Wrap Up

OVERVIEW

Types of Research

BENCH RESEARCH

- No identifiable human or animal materials
- Must comply with FDA Good Laboratory Practice (GLP) regulations if it will support or is intended to support application(s) to FDA
- Must still comply with PHS regulations if federally-funded
- No IRB or IACUC; other internal committees (conflicts, etc.)

ANIMAL RESEARCH

- Research on animals
- Must comply with Animal Welfare Act
- Institutional Animal Care and Use Committee (IACUC) oversight
- Must comply with FDA GLP regulations if it will support or is intended to support application(s) to FDA

OTHER RESEARCH / ACTIVITIES

- Development of software and other technologies
  - Not currently subject to FDA regulation
  - May be subject to other laws, including FTC Act, state consumer protection laws, HIPAA, etc.
- Biobanking
  - Act of creating biobank is a research activity
  - Must comply with applicable privacy and human subject protection laws (e.g., HIPAA, "Common Rule," state privacy and human subject protection laws, etc.
  - Institutional Review Board (IRB) oversight

CLINICAL RESEARCH

- Human Subjects
- Must comply with "Common Rule" if federally funded
- May need to comply with the Belmont Report or Declaration of Helsinki
- Privacy (e.g., HIPAA, state privacy laws)
- State Human subject protection laws
- Must comply with FDA Good Clinical Practice (GCP) regulations if it involves an FDA regulated product or will be submitted to or is held for inspection by FDA
- IRB oversight

Clinical Trials or Studies

- Voluntary research studies conducted in people and designed to answer specific questions about the safety or effectiveness of drugs, vaccines, other therapies, or new ways of using existing treatments
- Research involving a *living individual* about whom an investigator:
  - Obtains information or biospecimens through intervention or interaction with the individual and uses, studies or analyzes the information or biospecimens

  or

  - Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens

“Clinical Investigation”

- “a clinical investigation or research **involving one or more subjects** to **determine the safety or effectiveness of a device**” 21 C.F.R. § 812.3(h)
- “any experiment that **involves a test article** and **one or more human subjects** and that either is **subject to requirements for prior submission** to the Food and Drug Administration under section 505(i) or 520(g) of the act, **or** is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but **the results of which are intended to be submitted later to, or held for inspection** by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies” 21 C.F.R. § 50.3(c)

ClinicalTrials.gov

- Controlled clinical investigations (other than phase 1 investigations) of any U.S. Food and Drug Administration (FDA)-regulated drug or biological product for any disease or condition
- Certain studies of FDA-regulated medical devices, excluding small clinical trials to determine feasibility and certain clinical trials to test prototype devices, but including FDA-required pediatric postmarket surveillance

FDAAA, Section 801 and 42 C.F.R. Part 11

ClinicalTrials.gov (cont'd)

- The trial has one or more sites in the U.S.
- The trial is conducted under an FDA investigational new drug application or investigational device exemption
- The trial involves a drug, biologic, or device product that is manufactured in the U.S. or its territories and is exported for research

INVESTIGATIONAL DEVICE EXEMPTION (IDE)

Investigational Device Exemption (IDE)

- Allows investigational (uncleared or unapproved) device or a modified device to be used in clinical study **to collect safety and effectiveness data**
- Do not have to comply with traditional device regulation
- Investigational plan
- Informed consent
- Labeling for investigational use only
- Study monitoring
- Records and reports

IDE Application

- Name and address of sponsor
- Report of prior investigations (all prior clinical, animal, and laboratory testing)
- Investigational plan
- A description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and installation of the device
- An example of the agreement to be signed by the investigators and a list of the names and addresses of all investigators. Information that must be included in the written agreement are found in 21 C.F.R. § 812.43
- Certification that all investigators have signed the agreement, that the list of investigators includes all investigators participating in the study, and that new investigators will sign the agreement before being added to the study
- A list of the names, addresses, and chairpersons of all IRBs that have or will be asked to review the investigation and a certification of IRB action concerning the investigation (when available)
- The name and address of any institution (other than those above) where a part of the investigation may be conducted
- The amount, if any, charged for the device and an explanation of why sale does not constitute commercialization
- Please note that an environmental assessment as required under 21 CFR 25.40 or a claim for categorical exclusion under 21 CFR 25.30 or 25.34 is no longer required. [§25.34(g)]
- Copies of all labeling for the device
- Copies of all informed consent forms and all related information materials to be provided to subjects as required by 21 CFR 50, Protection of Human Subjects
- Any other relevant information that FDA requests for review of the IDE application. Information previously submitted to FDA in accordance with Part 812 may be incorporated by reference

FDA IDE Decisions

- **Approval** – sponsor may begin subject enrollment upon receipt of IRB approval and in accordance with the limits described in FDA's decision letter
- **Approval with Conditions** – sponsor may begin subject enrollment upon receipt of IRB approval and in accordance with the limits described in FDA's decision letter, including the maximum numbers of U.S. subjects and investigational sites, and must submit information addressing the issues identified as conditions of approval in FDA's letter within 45 days
- **Disapproval** – sponsor may <u>not</u> initiate enrollment in the clinical
- investigation until the sponsor submits an amendment to the IDE to respond to the deficiencies identified in FDA's letter and subsequently receives a new letter from FDA granting approval or approval with conditions

IDE-Exempted Research

- Products **on market before May 28, 1976** (when used consistent with indications in labeling) or devices FDA has found to be **substantially equivalent** to them
- **Certain diagnostics** (noninvasive, does not introduce energy, not used as primary diagnostic)
- **Consumer preference testing**, **testing of modifications** if testing is not for purpose of determining safety or effectiveness
- **Veterinary use** or for **animal research**
- **Certain custom devices** (subject to 21 CFR 812.2(b)), unless used to determine safety or effectiveness for commercial distribution

Nonsignificant Risk (NSR) Device Studies

- Abbreviated IDE requirements, but IDE not required (21 C.F.R. § 812.2(b))
- (1) not intended as an implant nor presents a serious risk to the health, safety, or welfare of a subject;
- (2) is not purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- (3) is not for use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health nor presents a potential for serious risk to the health, safety, or welfare of a subject;
- (4) nor otherwise presents a potential for serious risk to the health, safety, or welfare of a subject

Early Feasibility Studies (EFS)

- "may be used to evaluate the **device design concept** with respect to initial clinical safety and device functionality in a **small number of subjects** (generally fewer than 10 initial subjects) when this information cannot practically be provided through additional nonclinical assessments or appropriate nonclinical tests are unavailable."
- May guide device modifications, i.e., does not necessarily involve first clinical (in-human) use
- Except for high-risk devices, not subject to an IDE
- Must comply with 21 CFR Part 50 (Protection of Human Subjects) and Part 56 (Institutional Review Boards)

PRE-SUBMISSION MEETINGS & AGREEMENT MEETINGS

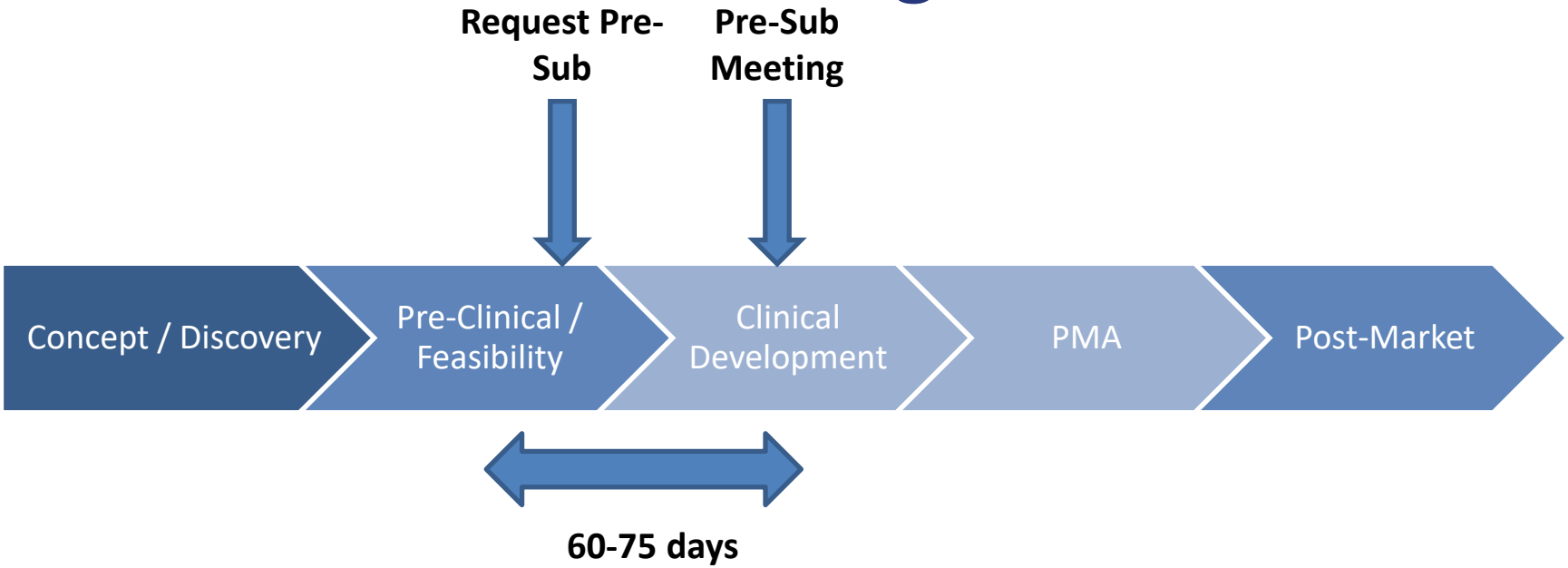
History

- Pre-IDE meetings were established in 1995 as opportunity to get feedback on future IDE application prior to submission
- Program evolved to include other opportunities for feedback for other premarket submissions
- MDUFA II included provisions to institute a structured process for managing these interactions (Pre-Submissions, or “Pre-Subs”)
- The process has evolved as a part of the broader Q-Submission (Q-Sub) Program, which now includes (Pre-Subs and other regulatory meetings)

Pre-Submission Meeting Basics

- Formal request for feedback from FDA in the form of formal written response or formal written feedback followed by meeting in which any additional feedback or clarifications are documented in meeting minutes
- Feedback in 70 days or 5 days prior to scheduled meeting, whichever is sooner
- Meet can be in-person or by teleconference – 1 hour
- Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program contains detailed guidelines for format and content of request

Typical Time to Request a Pre-Sub Meeting



Pre-Sub Purpose and What to Expect

- Mechanism for FDA to provide **one-time advice** (i.e., not iterative)
- Amendments or Supplements may be appropriate in light of new information
- Non-binding but FDA “intends to stand behind their feedback”
- Does not guarantee clearance or approval
- First consider whether different meeting or request is more appropriate (e.g., Study Risk Determination, Formal Early Collaboration)

Pre-Sub: What It Is NOT

- Request for general information or questions
- Request for FDA to design study protocols or clinical trial design for applicants
- Substitute for conducting your research and analysis of current medical device development practices
- Addressing questions that FDA reviewer could readily answer
- Interactive review of an active submission
- Appeal regarding a decision on a prior PMA submission
- Request for jurisdictional designation (RFD)
- Request for device classification (Section 513(g))
- Other mechanism of feedback

KEY PLAYERS, ROLES & RESPONSIBILITIES

Key Players

- Sponsor
- Investigator
- Institutional Review Boards (IRBs)
- Contract Research Organization (CRO)
- Site Management Organization (SMO)
- Site

What is a "Sponsor"?

- "Sponsor" is a formal term of art under the FDA regulations and identifies the responsible party to the FDA for a specific study
  - Sponsors have enumerated obligations under FDA regulations; holds the IDE / IND / BLA
- For non-FDA regulated studies, Sponsor is the person at whose direction or request the study takes place
- Think of the Sponsor's role as like a conductor…responsible for making the music sound right, leads all the different parts…the one in charge
- Note that an investigator may serve as the sponsor for investigator-initiated studies

Practice Tip: providing in-kind or financial support alone does not make a person or entity a "Sponsor"; sometimes the person/entity is just a "Funder"

Sponsor Responsibilities

- Obtains Investigational Device Exemption (IDE)
- Provides investigational product
- Registers with ClinicalTrials.gov
- Makes financial disclosures
- Selects sites, investigators
- Obtains IRB review and approval
- Consents subjects (21 CFR Part 50) and monitors study
- Maintains records and makes reports to IRB and FDA

What is an “Investigator”?

- An investigator is a scientist or medical professional responsible for conducting a research study (or certain responsibilities thereunder)
  - A Principal Investigator (PI) is the lead investigator for the study
  - Sub-investigators provide support to the PI in connection with the study
- For investigator-initiated studies, the investigator is the Sponsor
  - For example, investigator may apply to a drug manufacturer for a grant to conduct a research study to enhance scientific understanding of a disease for which the manufacturer currently has an approved therapeutic. The agreement designates the manufacturer the “funder” and the investigator as the “sponsor” for purposes of FDA regulations

Investigator Responsibilities

- Directs administration of investigational product and disposes of product
- Makes financial disclosures
- Supervises and directs sub-investigators and study staff
- Certain recordkeeping and reporting requirements
- Consents subjects
- Monitors study and subjects
- Signs investigator agreement
- Ensures investigation is conducted according to signed agreement, investigational plan, and FDA regulations

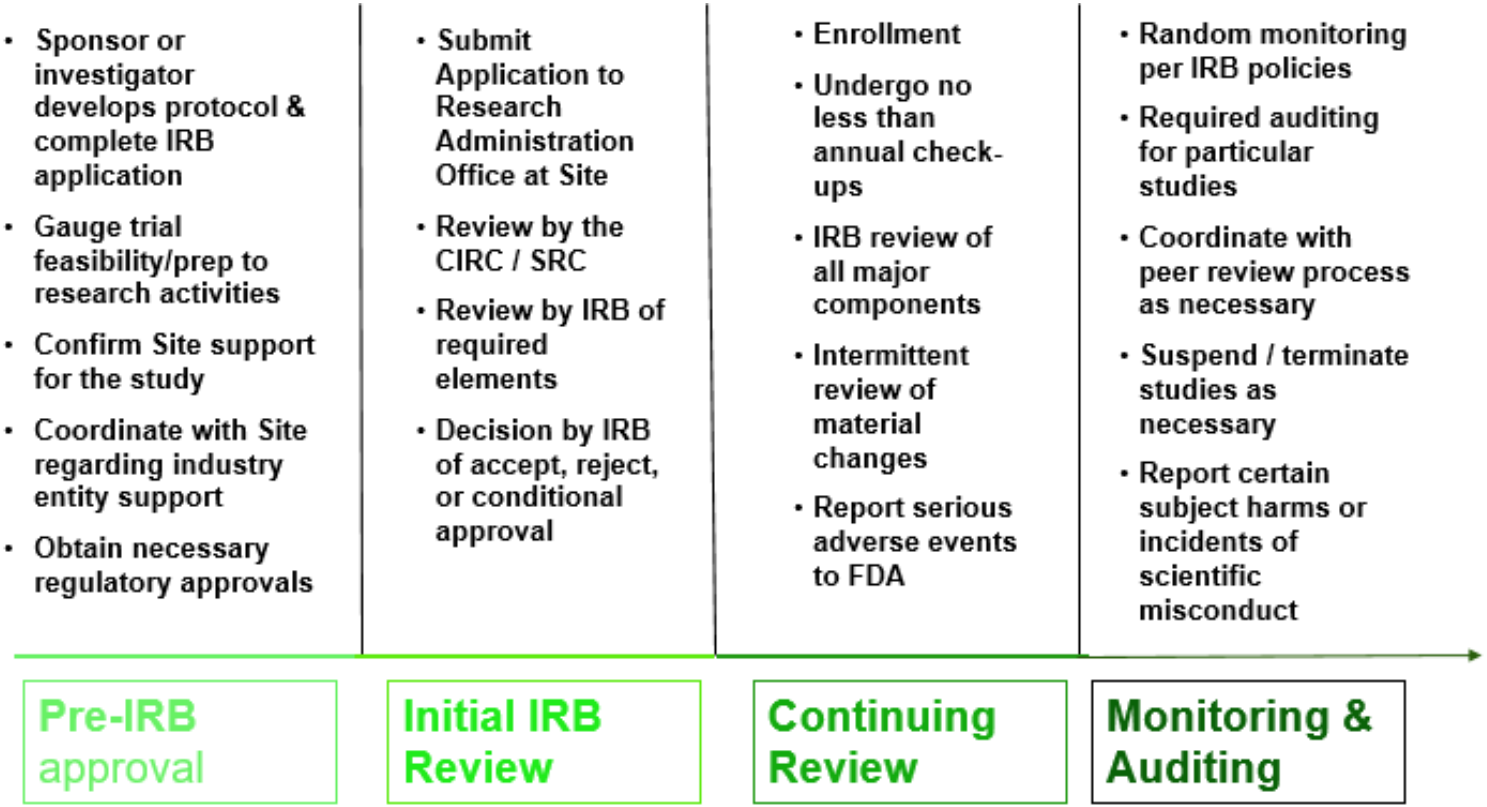
What is an “IRB”?

- The IRB is a group of scientists and non-scientists that convenes to review, approve, and continuously monitor studies that involve human subjects
  - May be internal (e.g., a hospital’s own IRB overseeing research conducted at the hospital) or external (e.g., a commercial IRB or other research site’s IRB overseeing research conducted elsewhere)
- Primary responsibility: To protect the rights and welfare of subjects
- IRBs have enumerated obligations under (as applicable):
  - Federal Food, Drug, and Cosmetic Act and its implementing regulations
  - The Common Rule (45 C.F.R. Part 46)
  - HIPAA
  - Institutional policies and procedures and Federalwide Assurance (FWA) with HHS

IRB Responsibilities

- Responsibilities include
  - Reviewing investigator qualifications and adequacy of sites
  - Determining whether IDE is needed, making NSR and informed consent waiver determinations
  - Reviewing and approving research (protocol, consents, subject recruitment materials & incentives for enrollment)
  - Continuing review (deviations, adverse events, records, reports)

Lifecycle of a Clinical Investigation



What is a “CRO”? An “SMO”?

- A **Contract Research Organization** (also Clinical Research Organization) (CRO) is an entity that contracts to provide support and oversight of research studies
  - Industry entities outsource to CROs various types of responsibilities (clinical and non-clinical)
  - Industry entities also at times delegate to CROs their “sponsor” responsibilities under FDA laws
- A **Site Management Organization** (SMO) sometimes refers to an independent entity that is retained, typically by an industry sponsor, to monitor compliance with a study protocol
  - SMOs typically have access to all detailed medical and research record information for this purpose
  - Some SMOs are formed by sites to serve as a centralized point of contracting and coordination with sponsors and CROs and in an effort to enhance trial opportunities

What is a “Site”?

- A “Site” is where a research study is conducted
  - E.g., hospital, physician practice, research institution
  - Consider: ResearchKit and other studies conducted through digital platforms
- Note: A hospital site’s provision of assistance to an investigator to enable the investigator to fulfill his/her responsibilities should not be considered an assumption of investigator’s responsibilities by a hospital site

GOOD CLINICAL PRACTICE (GCP) HIGHLIGHTS

Informed Consent

- (1) Statement that the study involves research, explanation of purposes, expected duration, description of procedures, identification of experimental procedures
- (2) Description of reasonably foreseeable risks or discomforts
- (3) Description of benefits to subject or others (or lack thereof)
- (4) Disclosure of appropriate alternative procedures or treatment (if any)
- (6) For research involving “more than minimal risk,” explanation as to whether compensation or medical treatments are available if injury occurs and how to access
- (7) Contact information for subject questions about research, subject rights, or injury
- (8) Statement that participation is voluntary and subject may discontinue participation

Informed Consent – Additional Elements

- Statement that the treatment/procedure may involve risks to subject, embryo, or fetus that are unforeseeable
- Anticipated circumstances under which participation may be terminated by investigator
- Additional costs to subject that may result from participation
- Consequences of withdrawal and procedures for termination
- Statement that significant new findings that may relate to subject's willingness to participate will be provided
- Approximate number of subjects involved

Informed Consent – Waivers & Emergency Use

Waivers

- "no more than minimal risk" (e.g.,
- Will not adversely affect rights and welfare of subjects
- Clinical investigation could not practicably be carried out without waiver or alteration (e.g., biospecimens)
- When appropriate, subjects will be provided with additional information after participation

Emergency Research

(21 C.F.R. § 50.24)

- (1) provides individuals in life-threatening situations access to potentially life-saving therapies;
- (2) advances knowledge through collection of information about effectiveness and safety; and
- (3) improves therapies used in emergency medical situations that currently have poor clinical outcomes.

IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects

Financial Disclosures

- Sponsors must collect and report (21 CFR Part 54)
- To identify financial interest as potential source of investigator bias in clinical studies
- But **Reportable ≠ Prohibited**

- Compensation affected by outcome of study
- Significant equity interest (during + 1 year following study completion)
- Proprietary interest in test article
- “Significant payments of other sorts” over $25,000

Adverse Event Reporting

- Unanticipated device effects: after evaluating, Sponsor must report results to FDA and reviewing IRBs (21 CFR § 812.150)
- Distinct from post-market medical device reports (MDRs)

Records & Reports

- **Records**
  - Name/intended use of device, objectives of investigation, information about investigators and IRBs, statement of extent to which good manufacturing practices will be followed, other information
  - Complaints and adverse device effects
- **Reports**
  - Unanticipated Adverse Device Effects
  - Withdrawal of IRB or FDA approval
  - Progress reports
  - Recalls and device disposition
  - Final report

PROHIBITION ON PRE-APPROVAL PROMOTION & COMMERCIALIZATION

Pre-Approval Promotion

- No claims should be made, either explicitly or implicitly, that the device is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other device.
- Cannot commercialize an investigational device by charging the subjects or investigators a higher price than that necessary to recover costs of manufacture, research, development, and handling.
- Unduly prolonging an investigation. If data developed by the investigation indicate that premarket approval (PMA) cannot be justified, the sponsor must promptly terminate the investigation.

See 21 C.F.R. § 812.7.

Pre-Approval Promotion (cont'd)

Sponsor *may*:

- Advertise for purposes of subject recruiting (with IRB review and approval)
- Engage in "scientific exchange"
  - Clearly non-promotional
  - Conducted by individuals who are scientifically trained
  - In a forum or context conducive and reflective of scientific in discussion
  - Example: interim clinical trial results may be presented, but must adhere to a strictly factual presentation and remember that **FDA prohibits representing in a promotional context that an investigational device is safe or effective for the purposes for which it is under investigation or otherwise promoting the device**

Medical Device Promotion

Type	Permitted Promotion	Source / Authority
No 510(k) or PMA pending	No promotion permitted	FDA interpretation of 21 U.S.C. § 360(k), evidenced by Warning Letters for promotions without pending 510(k) application.
New 510(k) pending	May promote for intended uses covered in pending 510(k) submission only; may not solicit or accept purchase orders.	U.S. Food and Drug Admin., "CPG Sec. 300.600 Commercial Distribution with Regard to Premarket Notification (Section 510(k))" (Sept. 24, 1987).
Approved IDE	Label with "Caution – INVESTIGATIONAL DEVICE, LIMITED BY FEDERAL (OR UNITED STATES) LAW TO INVESTIGATIONAL USE."	21 C.F.R. § 812.7; U.S. Food and Drug Admin., "Guideline for Preparing Notices of Availability of Investigational Medical Devices," (Feb. 1999). See also U.S. Food and Drug Admin., "Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects" (Mar. 19, 1999).
New PMA pending	Label with "Caution – INVESTIGATIONAL DEVICE, LIMITED BY FEDERAL (OR UNITED STATES) LAW TO INVESTIGATIONAL USE."	See above
New 510(k) pending (IDE)	Label with "Caution – INVESTIGATIONAL DEVICE, LIMITED BY FEDERAL (OR UNITED STATES) LAW TO INVESTIGATIONAL USE."	See above

Medical Device Promotion

Type	Permitted Promotion	Source / Authority
Available for sale under 510(k) clearance, but new use is under investigation or FDA review	May promote for previously cleared or approved uses only, unless the device would require a modification to perform the new use. If the latter, may promote for intended use with appropriate cautions (*e.g.*, "This device is currently undergoing premarket review by FDA for the [diagnosis/treatment] of [disorder]," if the claims can be substantiated by valid scientific evidence, but may not solicit or accept purchase orders.	Industry best practice
Available for sale under approved PMA, but new use is under investigation or FDA review	May promote for previously cleared or approved uses only.	Industry best practice
Foreign-approved only	Consider labeling with "Not Available for Sale in the United States." If manufactured abroad, may import with certification that it is for testing and evaluation and will be re-exported or destroyed afterward.	Industry best practice
Foreign approval for use different from approved used in U.S.	Consider promoting only for U.S.-approved use.	Industry best practice

BIORESEARCH MONITORING (BIMO) AND ENFORCEMENT ACTIONS

Bioresearch Monitoring (BIMO)

- Designed to monitor conduct and reporting of FDA-regulated research
- To ensure data integrity and quality
- To project rights and welfare of subjects
- Pre-approval inspection
- Labs, Investigators, Sites, IRBs

Investigator Restriction / Disqualification

- FDA can initiate when there is allegation investigator violated applicable regulations
- Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) and administrative hearing
- Disqualified investigators listed in public database
- Disqualified investigator **not eligible to receive investigational product** and is **not eligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA**
- Reinstatement only when “reasonable assurances” the investigator will comply with applicable laws

Clinical Hold

- Order issued by FDA to the sponsor of an IDE application to delay a proposed clinical investigation or to suspend an ongoing investigation
- FDA may place hold if an approved IDE represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation, taking into account the qualifications of the clinical investigators, information about the device, the design of the clinical investigation, the condition for which the device is to be investigated, and the health status of the subjects involved
- Sponsor may request by writing to FDA to remove the clinical hold, providing sufficient information to support the removal of such clinical hold (e.g., resolution of any issues)

Common Compliance Issues

- Failure to ensure proper monitoring
  - Study monitors failed to identify documentation irregularities (infusion of >1 subject at precisely same time impossible but documented)
  - Study monitors failed to identify deficiencies in drug accountability (e.g., same kit vial recorded as going to more than one patient)
- Failure to ensure that investigation conducted according to protocol
  - Blinding procedures not followed
  - Subjects enrolled who did not meet eligibility criteria

Common Compliance Issues (cont'd)

- Failure to secure investigator compliance with investigational plan
  - Patients did not begin dosing on same day as randomization – noted in monitoring visit but no follow-up
- Failure to ensure that only qualified investigators were selected
  - Sponsor selected investigator despite pre-study monitoring visit documenting that investigator is "not recommended" for lack of diligence, etc., and site not recommended because declined use of Spanish informed consent forms
- Failure to obtain proper informed consent
  - Subject enrolled prior to consent—wrong informed consent forms used for three subjects (sample form, not IRB-approved form)
  - Deliberate withholding of copy of informed consent forms from subjects

Common Compliance Issues (cont'd)

- Failure to promptly report to IRB all changes in research activity
  - Changes to examination frequency and adverse event review
- Failure to conduct the study according to the investigational plan
  - Baseline examinations not performed for some subjects
  - Investigator was to perform all clinical examinations, not sub-investigators – but sub-investigators performed some
- Failure to maintain adequate and accurate case report forms
  - Failed to contact subject who missed follow-up
- Failure to maintain adequate and accurate records of device disposition

Risks of Noncompliance

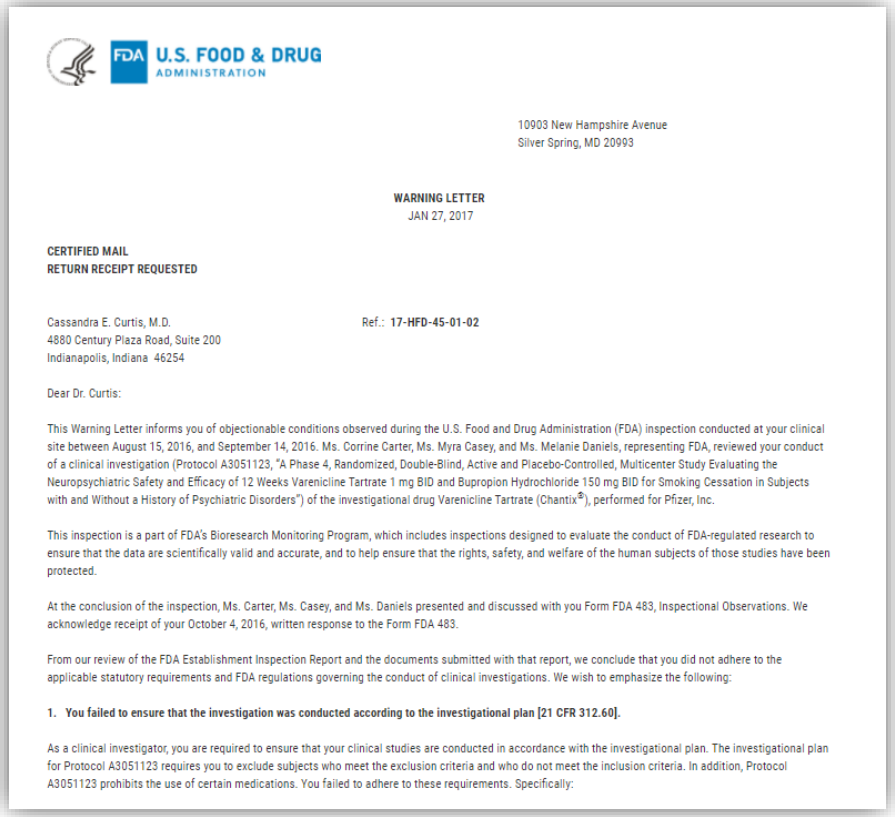
- Reputational harm
- Media Sanctions—loss of public confidence in research, clinical care, and the institution
- Board of Trustees/Directors liability
- Damage to other business relationships
- Liability under False Claims Act
- False Conflict of Interest certifications in applications for federal research grant
- Plaintiff lawsuits for injury/harm to human subjects (common law theories)
- Misrepresentation and fraud arising from failure to disclose conflict of interest
- Breach of fiduciary duty implied under informed consent
- Negligence, negligence *per se*
- Violation of right to be treated with dignity
- Assault/battery (subject did not consent to research as conducted)

Recent Enforcement Actions

- Majority of 483s and Warning Letters related to studies cited data integrity concerns (particularly foreign studies)
- Most frequent violations (2010-2019)
  - Sponsors: failure to ensure proper monitoring
  - IRBs: failure to prepare and maintain adequate documentation of IRB activities (incl. meeting minutes)
  - Investigators: failure to ensure investigation is conducted according to investigational plan

Example Investigator Warning Letter

- **"failed to ensure that the investigation was conducted according to the investigational plan"**
- **"failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation"**
- **"failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects"**



FDA U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

WARNING LETTER
JAN 27, 2017

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Cassandra E. Curtis, M.D.
4880 Century Plaza Road, Suite 200
Indianapolis, Indiana 46254

Ref.: **17-HFD-45-01-02**

Dear Dr. Curtis:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your clinical site between August 15, 2016, and September 14, 2016. Ms. Corrine Carter, Ms. Myra Casey, and Ms. Melanie Daniels, representing FDA, reviewed your conduct of a clinical investigation (Protocol A3051123, "A Phase 4, Randomized, Double-Blind, Active and Placebo-Controlled, Multicenter Study Evaluating the Neuropsychiatric Safety and Efficacy of 12 Weeks Varenicline Tartrate 1 mg BID and Bupropion Hydrochloride 150 mg BID for Smoking Cessation in Subjects with and Without a History of Psychiatric Disorders") of the investigational drug Varenicline Tartrate (Chantix®), performed for Pfizer, Inc.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Ms. Carter, Ms. Casey, and Ms. Daniels presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your October 4, 2016, written response to the Form FDA 483.

From our review of the FDA Establishment Inspection Report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We wish to emphasize the following:

1. **You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].**

As a clinical investigator, you are required to ensure that your clinical studies are conducted in accordance with the investigational plan. The investigational plan for Protocol A3051123 requires you to exclude subjects who meet the exclusion criteria and who do not meet the inclusion criteria. In addition, Protocol A3051123 prohibits the use of certain medications. You failed to adhere to these requirements. Specifically:

OTHER ISSUES & WRAP UP

Clinical Trial Equity

- **Generalizability** of results and to US population and applicability to US treatment practices by evaluating inclusion and exclusion criteria
- Recent FDA guidance on:
  - improving enrollment of participants from underrepresented racial and ethnic subgroups through eligibility criteria, enrollment practices & trial designs;
  - evaluation and reporting of age-, race-, and ethnicity-specific data in clinical studies;
  - inclusivity in medical product development
- Subgroup analysis plans to address potential differences based on demographics (gender, race, ethnicity)

Other Issues

- IRB suspension or termination of approval
  - Must be reported to FDA
- Vulnerable populations
  - Additional safeguards required under 21 CFR § 50.50
- Incentives for enrollment
  - Modest payments acceptable
  - Should be reviewed by IRB to avoid undue influence, disproportionate enrollment
- Foreign clinical data / studies not conducted under IDE
  - IRB or Independent Ethics Committee (IEC) review
  - Consents

Key Takeaways

- (1) Assess whether IDE requirement applies
- (2) Know which elements of GCP apply and identify your IRB
  - Be mindful of special considerations
- (3) Know your role and any unique responsibilities prescribed by law, regulation, or contract
- (4) Check debarment and disqualification lists before employing study personnel

Key Takeaways (cont'd)

- ❑ Have a robust investigator qualification process—ask questions about past compliance
- ❑ Make sure all parties understand their obligations, delegated or assumed – detail in contracts
- ❑ Be aware of potential affirmative obligations to study subjects in addition to proper informed consent
- ❑ Be aware of Sponsor obligations to supply adequate information to Investigators
- ❑ Institute robust monitoring and internal auditing mechanisms scaled to risks and nature of trials
- ❑ Institute adequate training for personnel involved in studies at all levels

Practical Tips for Management of Clinical Research

- Qualifications of Investigators and IRBs
  - Experience with products/therapeutic class being studied
  - Regulatory history with both U.S. and international regulators
  - Compliance with local laws
  - Knowledge of U.S. and foreign government requirements
- Pre-Engagement Clinical Trial Site/Investigator Visit
  - Adequate facilities
  - Standard Operating Procedures and Staff Training
  - IT systems and protocols (Part 11 compliance)

Practical Tips for Management of Clinical Research (cont'd)

- Clinical Trial Agreement
  - Define expectations for compliance with GCP
  - Nature and frequency of sponsor audits
  - Data sharing between sponsor and investigator
  - Responsibility for communicating with regulatory agencies
  - Payment and fair market value of services
- IRB Compliance
  - Confirm registrations
  - Review audit and FDA compliance history
  - Confirm experience with clinical trial category or products

Practical Tips for Management of Clinical Research (cont'd)

- Clinical Investigator Agreements
  - Understand that investigator is ultimately responsible for acts or omissions of delegee
  - Consider appropriate indemnification
- CRO Agreements
  - Define obligations assumed by CRO clearly
  - Understand regulations applicable to obligations assumed

Questions?

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